

OK TO ENTER: /S.A./ (05/18/2010)

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :  
BERNARD PAU, ET AL. : EXAMINER: AEDER, SEAN E  
SERIAL NO: 10/516,946 :  
FILED: AUGUST 9, 2005 : GROUP ART UNIT: 1642  
FOR: OXALIPLATIN ANTI- :  
RESISTANCE AGENT

REPLY BRIEF

COMMISSIONER FOR PATENTS  
ALEXANDRIA, VIRGINIA 22313  
SIR:

This Reply Brief responds to the Examiner's Answer mailed February 22, 2010. Both obviousness rejections, Issue A and Issue B, are addressed by the remarks below.

Starting at line 4 of page 9 of the Examiner's Answer ("EA") the Examiner urges that "a reduced level of expression of Bax gene correlating with enhanced resistance to oxaliplatin is rendered obvious". MacPherson is relied upon for teaching that knocking out the expression of Bcl-xl enhances oxaliplatin toxicity by enhancing apoptosis (programmed cell death). Chao, pages 821 and 826 are cited as teaching that Bcl-xl represses a common apoptosis pathway: "the transgenic Bcl-xl. . . displays substantial heterodimerization *in vivo* with the death-promoting molecule Bax", p. 826, top of col. 1. The Examiner concludes that the colorectal cancer cells expressing less Bax of Maurer, et al. would have been expected to be more resistant to oxaliplatin than cells expressing more Bax. However, this argument does not explain why these references would have provided a reasonable expectation of success that "reduced expression of said effector or marker gene [Bax, Bak] in said cancer

cell compared to said control cell indicates that said cancer cell is resistant to oxaliplatin” as required by claim 1 on appeal. The Examiner has cobbled together disparate teachings that reducing or eliminating Bcl-xl expression provides oxaliplatin resistant cells and that transgenic Bcl-xl can heterodimerize with Bax (a promoter of apoptosis) and inactivate it, at least when >50% of the Bax is heterodimerized with Bcl-2 or Bcl-xl. As previously argued Chao is concerned with a different parameter: the heterodimerization of Bax and Bcl-2 and Bcl-xl.

However, the Examiner has not established that cells expressing lower, reduced levels of Bax or Bak are more resistant to oxaliplatin. Moreover, while the Examiner’s analysis considers the effects of knocking out Bcl-xl expression as correlating with oxaliplatin resistance, it does not establish any direct connection between lower Bax expression and oxaliplatin resistance. Maurer did not disclose all the method steps of the present invention, specifically the comparisons between gene expression of pro-apoptotic Bax and/or Bak proteins in cancer cells and gene expression in control cells not resistant to oxaliplatin. That is, these references, do not suggest that a reduced level of expression of Bax gene alone correlates with enhanced resistance to oxaliplatin.

On page 10 of the EA, the Examiner attempts to both distinguish the invention from, but also relate the claim language to the teachings of Chao regarding the distinct heterodimerization parameter it teaches, i.e., the heterodimerization of Bax to Bcl-2 or Bcl-xl. To distinguish from this reference, the Examiner states lines 7-8 of page 10 that the rejection is “not based solely on Chao et al.”, however, this does not address the disparate and non-analogous heterodimeric ratio parameter teachings of Chao from the invention which simply requires determining the relative amount of Bax and/or Bak in a tumor cell. At the bottom of page 10 the Examiner states that “based on the cited references, a high level of pro-apoptotic Bax would be indicative of sensitivity to oxaliplatin. However, this section does not point

out support for the correlation of high levels of Bax and oxaliplatin sensitivity in the prior art references. This teaching is not in MacPherson, which involves Bcl-xl and oxaliplatin resistance, not in Chao, which teaches the importance of the heterodimerization and ratio of Bcl-xl to Bax, or in Maurer which fails to provide a nexus between oxaliplatin resistance and relatively higher levels of Bax and contemplates a different parameter involving the relative levels of Bax to Bcl-2 in col. 1 of page 2642. “When Bcl-2 is in excess, Bax/Bcl2 heterodimers are formed, and cells are protected against programmed cell death. . .In the case of Bax predomination, Bax homodimers are formed, and cells are susceptible to programmed cell death”. Maurer’s statement that “Bax homodimers are formed” when there is a high level of Bax conflicts with the Examiner’s speculations starting at line 8 of page 11 that “there will be free Bax” when Bax is expressed at a low, weak level, but Bcl-xl is expressed at an even lower level. Despite, the Examiner’s attempt to turn the Maurer teachings regarding ratios of Bax and Bcl-2 into the invention, Maurer simply does not disclose that a cancer cell having a higher level of Bax than a control cell would be resistant to oxaliplatin. On the other hand, the invention as claimed by claim 1 requires “reduced expression of said effector or marker gene [Bax and/or Bak] in said cancer cell compared to said control cell indicates that said cancer cell is resistant to oxaliplatin”. Accordingly, for the additional reasons discussed in the response to the Examiner’s arguments, this rejection cannot be sustained.

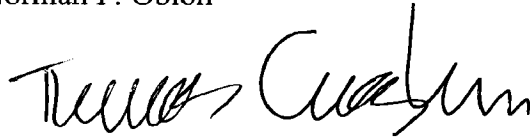
RELIEF REQUESTED

The Appellants respectfully request reversal of the grounds of rejection above and the allowance of this application.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,  
MAIER & NEUSTADT, P.C.  
Norman F. Oblon

Customer Number  
22850

A handwritten signature in black ink, appearing to read "Thomas M. Cunningham". The signature is fluid and cursive, with the first name "Thomas" and last name "Cunningham" clearly distinguishable.

Thomas M. Cunningham  
Registration No.: 45,394